REMARKS

The claims in the application are claims 6, 7, 10-16, 23-26, 28 and 29. Claims 1-5, 8, 9, 17-22, and 27 have been cancelled.

The examiner has rejected claims 6, 7, 10-16 and 29 under 35 U.S.C. Section 102(a) as being anticipated by Alberto et al (J. Am. Chem. Soc., 1998, 120, pp. 7987-7988). By the above amendments to the claims, this rejection has been overcome. The reference does not disclose or suggest the presently claimed non-aromatic ligands to be employed in a useful imaging fluid. In fact, the reference teaches away from such ligands in the following statement from the reference found at p. 7988, second column: "Although PADA could stabilize intermediate oxidation states (as found with its fragment imino-N,N-diacetic acid[17] or pyridine[18]), such behavior was not observed and 3 (^{99m}Tc) formed in quantitative yield."

As can be seen from the enclosed copy (see Appendix) of the Blauenstein publication (footnote 17 of Alberto) referenced in the above quoted portion of Alberto, the compounds employed by Blauenstein are unrelated to the compounds of the present claims. Most importantly the compounds of Blauenstein do not contain carbonyls as now claimed. Accordingly, the above quoted remark in Alberto with respect to the fragment IDA has no relevance to the present invention.

The entire reference, taken as a whole is a demonstration of the surprising and novel discovery of the present inventor, i.e., that non-aromatic aminopolycarboxylates will not only stabilize the desired form of Tc carbonyl but also provides unexpected advantages over aromatic counterparts.

Such surprising and unexpected advantages are noted in the specification at p. 4 and also demonstrated by the data in the present application as filed. The data in Tables 3, 4 and 5

reporting the biodistribution of the Octreotate indicate a high proportion located in the kidneys while also indicating receptor specific activity. It is particularly demonstrated in Table 5 that the kidney clearance is about doubled for the claimed compound over the prior art Histamine. This result is noted in the text of Example 6. What this data translates to is the safety and efficacy of the novel ligands. By being taken up by the kidneys there is evidence that the body will safely eliminate the radionuclide quickly and safely rather than being taken up by liver where longer disposal rates are widely known in the art.

Accordingly, not only does Alberto et al. not teach or suggest the present invention, it actually teaches away from it by including an aromatic fragment. Such disclosure places emphasis on the surprising and unexpected results now found by the present inventor. The elimination of an aromatic component in these carbonyls is not taught or suggested in the prior art.

Accordingly, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. Section 102(a) in view of the above amendments and remarks.

The Examiner has rejected claims 6, 23, 24, 26, 28, and 29 under 35 U.S.C. Section 103(a) as being unpatentable over Alberto et al., cited above, for reasons of record in the Office Action of Feb. 5, 2003 as well as for reasons stated in the above noted rejection under 35 U.S.C. Section 102(a). As noted above, not only does Alberto et al. not disclose or suggest the use of the non-aromatic ligands of the present invention, Alberto et al. teaches away from the present invention. The above remarks with respect to the rejection under 35 U.S.C. Section 102(a) are repeated here with respect to the rejection under 35 U.S.C. Section 103(a). Furthermore, the inventor now teaches a new class of ligands with unexpected advantages over ligands of the type actually taught by Alberto. The present invention provides a new class of ligands heretofore

believed to be unsuitable. Such facts fully support the non-obviousness of the present invention. It has long been held that aromatic compounds are patentably distinct from non-aromatic compounds. The presently claimed non-aromatic compounds are therefore not obvious in view of the prior art of Alberto et al. Accordingly, the Examiner is respectfully requested to withdraw the rejection of claims 6, 23, 24, 26, 28, and 29 under 35 U.S.C. Section 103(a) on the basis of Alberto et al.

THE NEW REJECTION

The Examiner, in view of applicants amendment, has newly rejected claims 6, 7, 10-16, 23, 24, 26, 28, and 29 under 35 U.S.C. Section 103(a) on the basis of Alberto et al. (WO 98/48848) (hereinafter referred to as "Reference I") in view of Alberto et al. (J. Am. Chem. Soc.) (hereinafter referred to as "Reference II"). This rejection is traversed for the following reasons.

While it is true that the "Reference I" does not teach or suggest the non-aromatic ligands of the present invention, it is respectfully submitted that "Reference II" does not supply such deficiency of "Reference I". "Reference II" discloses only aromatic ligands (PADA) as being useful. As noted above, "Reference II" notes that non-aromatic ligands fragments only stabilize "intermediate oxidation states" of Tc in non-carbonyl compounds. Thus, as noted above, the secondary reference not only does not supply the deficiencies of "Reference I" but also actually teaches away from the present invention and its unexpected advantages. It is further noted that the ligands listed in "Reference I" are not relevant to the present invention. In fact, Reference I" suggests the use of histadine (p.6, line 12) that is used for comparison in Tables 3, 4 and 5 of the present application. Thus, the surprising advantages of the present invention are shown over the

prior art of record. In view of the above amendments and remarks, it is respectfully requested that the newly applied rejection be withdrawn.

In view of the above amendments and remarks, it is respectfully requested that the Examiner allow the claims and pass the application to issue at the earliest opportunity.

If any issue regarding the allowability of any of the pending claims in the present application could be readily resolved, or if other action could be taken to further advance this application such as an Examiner's amendment, or if the Examiner should have any questions regarding the present amendment, it is respectfully requested that the Examiner please telephone Applicant's undersigned attorney in this regard.

Respectfully submitted,

Dated: April 15, 2004

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ATTORNEYS FOR APPLICANT

APPENDIX A

19.8

THE OXIDATION STATE OF TECHNETIUM IN AMINOPOLYCARBOXYLATE COMPLEXES

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Investigations concerned Tc complexes comprising the following ligands: iminodiacetate (IDA), nitrilotriacetate (NTA), ethylenediaminetetraacetate (EDTA) and diethylenetriaminepentaacetate (DTPA). These complexes are already known, and the oxidation number of Tc was hitherto considered to be either +IV (1, 2) or +III (3, 4, 5).

Synthesis of the complexes: Pertechnetate (Tc-99) was reduced by SO_2, Sn or $SnCl_2$ respectively, in presence of the ligands in slightly acidic solutions. Using SO_2 much more time was needed, but it was quite easy to get rid of interfering species. In all cases pink or purple solutions were obtained with an absorption maximum at nearly 500 nm and a molar extinction coefficient of 1000 to 2500 (Table 1).

Oxidimetric titrations, with Br_2 and BrO_3^- respectively, were possible only in presence of IDA as ligand and gave an oxidation number of +III for the metal ion. The complexes in neutral solutions were only absorbed by anion exchangers. Consequently, all complexes present must be negatively charged. The solid products, obtained by evaporation of the solvent under reduced pressure, showed a diamagnetic behavior, excluding clearly the presence of Tc(IV) and pointing to Tc(III). During the reduction only with EDTA a colorless intermediate is formed, detected by paper chromatography (rf=0.5) using acetonitrile/water (7:3; v/v) as eluent (6). In this intermediate Tc is present in a higher oxidation state than +III, may be +IV.

The behavior of the complexes of Tc-99 and Tc-99m with the same ligands was compared by paper chromatography (acetonitrile/water = 7:3 (v/v)). In all cases the same rf values resulted with Tc-99 and Tc-99m for solutions obtained by reduction by SO_2 and Sn. The rf values are listed in table 2. In the system EDTA-Tc-99m, only the intermediate product can be detected (rf=0.5). Tc-99m is virtually decayed completely, before the final complex is formed.

To elucidate the composition of the complexes the molar ratio of Tc:ligand was varied from 1:0,5 to 1:10. The resulting solutions were investigated by UV-VIS-spectrophotometry and paper chromatography. It can be concluded, that two complexes are formed with both IDA and NTA, i.e. the 1:1 complexes $TcIDA^+$ and TcNTA at low pH values and the 1:2 complexes $Tc(IDA)_2^-$ and $Tc(NTA)_2^{3-}$ in neutral or slightly acidic solutions. The other ligands seem to form only 1:1 complexes $TcEDTA^-$ and $TcDTPA^{2-}$. Alkalimetric titrations of the system Tc-NTA show a buffer region at pH=5÷6, corresponding to the reaction $TcNTA + HNTA^{2-} \rightarrow Tc(NTA)_2^{3-} + H^+$. The same reaction with IDA instead of NTA takes place at pH=3÷4. With EDTA as ligand, a protonated complex (HTcEDTA) seems to be formed at pH values lower than 2. In alkaline solutions decomposition of these complexes occurs, leading to the formation of hydrolytic products and oxidation of Tc(III).

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(5) Russel C.D. and Cash A.G., J. Electroanal. Chem., 92, 85 (1976).
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Table 1

Compl	
$TcIDA^+$	
TcNTA	
$TcEDTA^-$	
$TcDTPA^{2-}$	

Table 2

$TcIDA^+$	(
$TcEDTA^-$	
$TcDTPA^{2-}$	

Table 1. UV-VIS-Spectrophotometry: Maxima of the absorption of the Tc(III)-complexes with aminopolycarboxylates. (λ_{max}: nm; ε: l/mol cm)

Complex	λ_{max} (ε)	Complex	λ_{max} (ε)
$TcIDA^{+}$ (?)	330 (8300)	$Tc(IDA)_2^{-}$	515 (1300)
TcNTA	500 (2400)	$Tc(NTA)_2^{3-}$	515 (1500)
$TcEDTA^{-}$	500 (1950)	HTcEDTA	490 (2000)
$TcDTPA^{2-}$	490 (1540)		

Table 2. Paper chromatography: rf values with acetonitrile/water = 7:3 (v/v)

$TcIDA^{+}$(?)	: 0.25	$Tc(IDA)_2^{-}$	: 0.35	TcNTA	: 0.35	$Tc(NTA)_2^{3-}$	: 0.2
$TcEDTA^{-}$	: 0.35	HTcEDTA	: 0.55	Tc-EDTA-intermediate product		: 0.5	
$TcDTPA^{2-}$	: 0.2						

Derivative	Organ	I Normal	II Bile duct ligatured	III Hilum of liver ligatured	IV Urine in untreated rats	V Bile in untreated rats
2,6-Dimethyl-IDA	Liver	0.83	32.01	1.05	1,18	0.92
	Intestines with contents	84.08	3.37	14.60	67.77	76.35
	Kidneys	5.14	21.12	2.27	6.79	5.88
	Bladder with urine	7.74	13.28	0.12	18.34	12.58
	Thyroid	0.01	0.04	0.11	0,01	0.003
	1 ml blood	0.13	0,53	0.91	0.16	0.03
	Rest of body	6.94	34.90	83.05	11.74	4.92
2,6-Diethyl-IDA	Liver	2,53	38.98	4.18	2.89	0.36
	Intestines with contents	78,79	2.50	13.59	18,78	88.51
	Kidneys	4.47	14.65	3.78	14.87	3.55
	Bladder with urine	5.62	7.18	0.19	35.24	4.38
	Thyroid	0.009	0.025	0.08	0.035	0.004
	1 ml blood	0.18	0.61	1.32	0.48	0.03
	Rest of body	8.14	36.60	80.36	30,42	3.70
4-n-Butyl-IDA	Liver	3.86	66.62	1.39	3,34	2.58
	Intestines with contents	83.56	1.91	15.79	59.70	86.69
	Kidneys	2.75	3.03	5.23	5.76	2.11
	Bladder with urine	1.78	3.00	0.10	11.50	4.34
	Thyroid	0.01	0.03	0.12	0.04	0.008
	1 ml blood	0.29	0.96	2.48	0.26	0.04
	Rest of body	10.28	24.83	74.09	19.97	5.90
4-n-Pentyl-IDA	Liver	12.47	80.65	1.93	3.22	8.34
	Intestines with contents	85.39	1.27	14.09	20.88	80.25
	Kidneys	0.96	1.95	4.98	16.91	1.24
	Bladder with urine	0.13	0.16	0.11	36.98	0.73
	Thyroid	0.004	0.01	0.12	0.04	0.008
	1 ml blood	0.05	0.47	2.72	0.29	0.05
	Rest of body	3.11	11.34	73.51	17.81	3.62
2,4,5-Trimethyl-IDA	Liver	1.70	40.60	2.64	1.60	1.33
	Intestines with contents	80.57	2.80	12.90	54.96	55.49
	Kidneys	2.28	10.70	3.07	3.70	2.49
	Bladder with urine	5.74	12.54	0.17	15.00	32.85
	Thyroid	0.01	0.03	0.07	0.02	0.007
	1 ml blood	0.17	0.73	1.78	0.22	0.09
	Rest of body	9.70	37.47	84.64	15.54	10.60

19.9

Studies of the pharmacokinetics of various Tc-99m-IDA derivatives

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The pharmacokinetics of technetium-99m-acetanilidoiminodiacetate (IDA) derivatives is influenced to a very large degree by substituents introduced on the aromatic ring (1-5). As extensive studies in our laboratory have shown, the differences in their distribution in the organs and in their liver kinetics cannot be explained solely by differences in their lipophilic character or differences in the strength of the protein binding. Thus, for example, 2,6-dimethyl-IDA and pentafluoro-IDA are both strongly hydrophilic and subject to only weak protein binding, but nevertheless, they exhibit large differences in pharmacokinetics:

		2,6-dimethyl-IDA	pentafluoro-IDA
Rabbit:	t_{max} (liver)	5.2 min.	14.3 min.
	$t_{1/2}$ (liver)	9.5 min.	48.7 min.
Rat:	renal cumulation 30 min. p.i.	4.9 %	1.6 %

In order better to assess the urinary elimination rate we have sought an animal model with which to simulate liver insufficiency. An attempt to obtain such a model through ligation of the entire hilum of the liver (hepatic vein, hepatic artery and bile duct) was unsuccessful. As studies with I-131-Hippuran have also clearly shown, this surgical procedure in the rat also causes the total collapse of renal function (table, column III).

However, ligation of the ductus choledochus in rats yields quite a good animal model for obstructive jaundice. This occlusion prevents the flow of bile from the liver, which slows the liver's uptake of the radiopharmaceutical. The resulting increased concentrations in the plasma cause a higher cumulation of radioactivity in the kidneys and increased urinary elimination.

Comparison of the different derivatives shows that renal cumulation and the urinary elimination rate are not proportional (table, column I). Thus for the derivatives 2,6-dimethyl-IDA and 2,4,5-trimethyl-IDA, for example, renal cumulation (30 min. p.i.) is 4.9 and 2.1 %, respectively, while the ratio of the proportions of activity eliminated in the urine (30 min. p.i.), at 2.7 and 5.3 %, respectively, is reversed. It thus appears quite possible that, in addition to urinary elimination, some renal cumulation also occurs to a varying degree, depending on the particular derivative used.

One possible explanation for this remarkable behaviour is (at least partial) metabolization. Loberg et al. (6) investigated this question by reinjecting bile and urine in mice and came to the conclusion that 2,6-dimethyl-IDA is not metabolized. However, our corresponding experiments with 5 different IDA derivatives (table, column IV and V) in rats indicated that the portion of radioactivity which is eliminated with the urine is at least partially metabolized. This effect appears to be particularly evident for 2,6-diethyl-IDA and 4-n-pentyl-IDA. Chromatographic studies support this hypothesis. It was also shown by chromatography that these "metabolites" are not pertechnetate; accordingly thyroid cumulation following the reinjection of bile and urine remains low. There is nothing that can yet be said about the nature of the metabolites. These studies are being continued.

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Derivative
2,6-Dimethy
2,6-Diethyl
4-n-Butyl-2
4-n-Pentyl-
2,4,5-Trim IDA